REMARKS

Upon entry of the present Amendment, claims 11-12, 15, 18-20 and 22-24 will remain pending in the above-identified application and stand ready for further action on the merits.

Claims 1-10, 16-17, 25 and 27 stand withdrawn from consideration based on an earlier restriction requirement of the Examiner. Claims 11-12, 15, 18-20 and 23-24 have been amended. Claims 13-14 and 21 have been cancelled herein. The present amendments to the claims merely clarify the present invention and do not introduce new matter into the application as originally filed.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 13-15, 18, 21 and 23 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claims 13, 14 and 21 have been cancelled herein, which renders the rejection as to these claims moot.

First, the Examiner states that the term "agent" is unclear. Applicants have amended the claims under consideration at present to delete this term. Thus, Applicants respectfully submit that the amendment overcomes the outstanding rejection and that the rejection be removed.

Second, the Examiner argues that it is ambiguous as to what is the quantity of the required active ingredients embraced by the condition "improving a disease," "antagonist," and "agonist." Specifically, the Examiner alleges that "improvement" is relative and subjective and that it is unclear how a person's intellectual function can be improved. Applicants have amended the claims under consideration at present to remove the term "improving." Thus, Applicants

respectfully submit that the amendment overcomes the outstanding rejection and that the rejection be removed.

Third, the Examiner states that claim 23 is confusing as to how many compositions are encompassed by the claim. Claim 23 has been amended to more precisely claim the present invention in terms of a "method for treatment." Thus, Applicants respectfully submit that the amendment overcomes the outstanding rejection and that the rejection be removed.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 18-24 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner asserts that the present specification does not reasonably provide enablement for the "prevention" or "improvement" of the conditions recited in claims 18-24. The Examiner argues that "preventing" requires zero occurrence of a named condition and such scope cannot be achieved. The Examiner further argues that the term "improving" is subjective. Claim 21 has been cancelled herein, which renders the rejection as to this claim moot.

Applicants have amended claims 18 and 23 to remove the terms "preventing" and "improving." Thus, Applicants respectfully submit that the amendment overcomes the outstanding rejection and that the rejection be removed.

Claims 11-12 are also rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner asserts that the scope of the claims encompassing "hydrate" lacks sufficient description and enablement.

In order to further prosecution, Applicants have amended claims 11 and 12 to remove the term "hydrate." Thus, Applicants respectfully submit that the amendment overcomes the outstanding rejection and that the rejection be removed.

Rejection under 35 U.S.C. § 103(a)

Claims 11-15 and 18-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Sugimoto et al. '841 (U.S. Patent No. 4,895,841) supplemented with CA110:173102 in view of Iimura et al. '330 (U.S. Patent No. 6,677,330) supplemented with CA133:207817 and further in view of Kato et al. (Neuroscience Letters, 1999, vol. 260, p. 5-8); or Iimura et al. '330 in view of Sugimoto et al. '841 further in view of Kato et al. Claims 13-14 and 21 have been cancelled, which renders the rejection as to these claims moot. Applicants respectfully assert that the combination of Sugimoto et al. '841, Iimura et al. '330, and Kato et al. do not disclose each and every aspect of, at least, independent claim 11. Reconsideration and withdrawal of this rejection is respectfully requested based on the following considerations.

Legal Standard for Determining Prima Facie Obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

"There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obvious was held improper.).

"In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab,* 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee,* 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the

importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The Supreme Court of the United States has recently held that the teaching, suggestion, motivation test is a valid test for obviousness, but one which cannot be too rigidly applied. See *KSR Int'l Co. v Teleflex Inc.*, 127 SCt 1727, 82 USPQ2d 1385 (U.S. 2007). The Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, *ibid.*, reaffirmed the Graham factors in the determination of obviousness under 35 U.S.C. § 103(a). The four factual inquiries under Graham are:

(a) determining the scope and contents of the prior art;

(b) ascertaining the differences between the prior art and the claims in issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating evidence of secondary consideration.

Graham v. John Deere, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (U.S. 1966).

The Court in *KSR Int'l Co. v. Teleflex, Inc., supra.*, did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

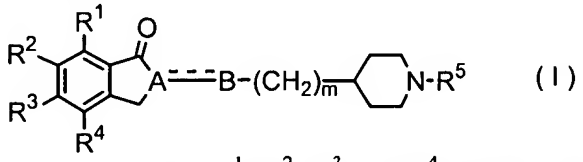
Even so, the Court in *KSR Int'l Co. v. Teleflex, Inc., ibid.*, rejected a rigid application of the "teaching, suggestion, or motivation" (TSM) test, which required a showing of some teaching, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art

to combine the prior art elements in the manner claimed in the application or patent before holding the claimed subject matter to be obvious.

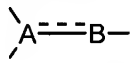
Further, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336, quoted with approval in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007).

The Present Invention and Its Advantages

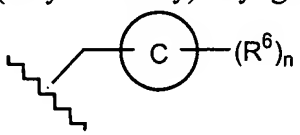
The present invention relates to specific indanone derivatives. As recited in instantly amended independent claim 11, the invention provides for:

> An indanone compound represented by the following formula (I) or a pharmacologically acceptable salt thereof:
>
> 
>
> (I)
>
> wherein R^1, R^2, R^3 and R^4 are the same as or different from each other and each represents hydrogen atom, a halogen atom, hydroxyl group, nitrile group, a C_{1-6} alkyl group which may be substituted, a cycloalkyl group having three to eight carbon atoms which may be substituted, a C_{1-6} alkoxy group which may be substituted, a cycloalkoxy group having three to eight carbon atoms which may be substituted, an acyl group having one to six carbon atoms which may be substituted, a C_{1-6} alkoxycarbonyl group which may be substituted, a C_{1-6} alkylaminocarbonyloxy group which may be substituted, a di(C_{1-6} alkyl)aminocarbonyloxy group which may be substituted, nitro group, an amino group which may be substituted, an amide group which may be substituted, mercapto group or a thio-C_{1-6} alkoxy group which may be substituted, and further

R^1 with R^2, R^2 with R^3, or R^3 with R^4 may together form an aliphatic ring, an aromatic ring, a heterocyclic ring or an alkylenedioxy ring; the partial structure:



represents a group represented by >CH-CH_2-, >C=CH- or >C(-R^7)-CH_2-; m represents an integer of 0 or 1 to 5; and R^5 represents hydrogen atom, a C_{1-6} alkyl group which may be substituted, a C_{2-6} alkenyl group which may be substituted, a C_{2-6} alkynyl group which may be substituted, a cycloalkyl group having three to eight carbon atoms which may be substituted, a 2,2-(alkylenedioxy)ethyl group or a group represented by the formula:



wherein the ring C represents benzene ring, an aliphatic ring or a heterocyclic ring; R^6s are the same as or different from each other and each represents hydrogen atom, a halogen atom, hydroxyl group, nitrile group, a C_{1-6} alkyl group which may be substituted, a C_{2-6} alkenyl group which may be substituted, a C_{2-6} alkynyl group which may be substituted, a cycloalkyl group having three to eight carbon atoms which may be substituted, a C_{1-6} alkoxy group which may be substituted, a C_{1-6} alkoxyalkoxy group which may be substituted, an aryloxy group which may be substituted or an aralkyloxy group which may be substituted, and further two of R^6s may together form an aliphatic ring, an aromatic ring, a heterocyclic ring or an alkylenedioxy ring; R^7 represents a halogen atom, hydroxyl group, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, nitrile group, a halogeno-C_{1-6} alkyl group, a hydroxyl-C_{1-6} alkyl group, a cyano-C_{1-6} alkyl group, an amino-C_{1-6} alkyl group, nitro group, azide group, an amino group which may be substituted, carbamoyl group which may be substituted, carboxyl group which may be substituted, mercapto group or a thio-C_{1-6} alkoxy group; and n represents an integer of 1 to 5, provided that 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine, a pharmacologically acceptable salt thereof or a hydrate of them are excluded;

wherein the indanone compound is one selected from:

(1) 1-benzyl-4-[[5,6-(1,2-ethylenedioxy)-1-indanon]-2-ylidene]methylpiperidine,

(2) 1-benzyl-4-[(5-cyclohexyl-1-indanon)-2-ylidene]methylpiperidine,

(3) 1-benzyl-4-[(5-cyclohexyloxy-6-methoxy-1-indanon)-2-ylidene]methylpiperidine,

(4) 1-benzyl-4-[[5-methoxy-6-(2-propyloxy)-1-indanon]-2-ylidene]methylpiperidine,

(5) 1-benzyl-4-[[5,6-(1,2-ethylenedioxy)-1-indanon]-2-yl]methylpiperidine,

(6) 1-benzyl-4-[[5,6-cyclohexyl-1-indanon]-2-yl]methylpiperidine,

(7) 1-benzyl-4-[(5-cyclohexyloxy-6-methoxy-1-indanon)-2-yl]methylpiperidine,
(8) 1-benzyl-4-[[5-methoxy-6-(2-propyloxy)-1-indanon]-2-yl]methylpiperidine,
(9) 1-benzyl-4-[(6-ethoxy-5-methoxy-1-indanon)-2-yl]methylpiperidine,
(10) 1-benzyl-4-[[6-methoxy-5-(1-propyloxy)-1-indanon]-2-yl]methylpiperidine,
(11) 1-benzyl-4-[(5-cyanomethoxy-6-methoxy-1-indanon)-2-yl]methylpiperidine,
(12) 1-cyclopentylmethyl-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(13) 1-cyclohexylmethyl-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(14) 1-cycloheptylmethyl-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(15) 1-cyclooctylmethyl-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(16) 1-(2-fluorobenzyl)-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(17) 1-(3-fluorobenzyl)-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(18) 1-(4-fluorobenzyl)-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(19) 1-(2-chlorobenzyl)-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(20) 1-(3-chlorobenzyl)-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(21) 1-(4-chlorobenzyl)-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(22) 1-(2-methylbenzyl)-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(23) 1-(3-methylbenzyl)-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(24) 1-(4-methylbenzyl)-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(25) 1-benzyl-4-[(6-ethoxy-5-methoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(26) 1-benzyl-4-[(5-ethoxy-6-methoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(27) 1-benzyl-4-[[6-methoxy-5-(1-propyloxy)-2-fluoro-1-indanon]-2-yl]methylpiperidine,
(28) 1-(2-fluorobenzyl)-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,

(29) 1-(3-fluorobenzyl)-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(30) 1-(4-fluorobenzyl)-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(31) 1-(2-chlorobenzyl)-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(32) 1-(3-chlorobenzyl)-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(33) 1-(4-chlorobenzyl)-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(34) 1-(2-methylbenzyl)-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(35) 1-(3-methylbenzyl)-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(36) 1-(4-methylbenzyl)-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(37) 1-cyclopentylmethyl-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(38) 1-cyclohexylmethyl-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(39) 1-cycloheptylmethyl-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(40) 1-cyclooctylmethyl-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(41) 1-benzyl-4-[(5-cyanomethoxy-6-methoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine,
(42) 1-(3,4-difluorobenzyl)-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(43) 1-(3,5-difluorobenzyl)-4-[(5,6-diethoxy-1-indanon)-2-yl]methylpiperidine,
(44) 1-(3,4-difluorobenzyl)-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine, and
(45) 1-(3,5-difluorobenzyl)-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine.

The invention set forth in pending independent claim 11 as well as dependent claims 12, 15, 18-20 and 22-24 is not taught or described in the cited art of record, as indicated below.

Distinctions Over the Cited Art

The Examiner alleges that Sugimoto et al. '841 and Iimura et al. '330 disclose acetylcholine esterase inhibitors structurally encompassing the instant claims. However, the claimed compositions are sigma receptor binding instead of AcCh esterase inhibiting. To overcome this deficiency, the Examiner cites Kato et al. to show that the indenolyl-piperidine compounds known to have AcCh esterase activity would be expected to have similar sigma receptor binding activity.

Applicants respectfully traverse the Examiner's interpretation of Kato et al. Kato et al. actually disclose that TAK-147, with a benzylpiperidine moiety but ***no indanone group***, had a high affinity for sigma receptors and is an acetylcholine esterase inhibitor. The findings of Kato et al. were largely limited to TAK-147. The only other compound listed as having a high affinity for sigma receptors and being an acetylcholine esterase inhibitor is donepezil, with a benzylpiperidine moiety similar to TAK-147. Kato et al. also note that other acetylcholine esterase inhibitors showed no effect on sigma receptors.

In stark contrast to the compounds of Kato et al., claim 11 recites compounds having a benzyl-piperidine group ***and an indanone group***. In fact, the present invention discloses donepezil as a control group in showing the superior results of the claimed invention (Tables 1 and 2 on page 42). Thus, the references fail to teach a "sigma receptor binding agent comprising an indanone compound" selected from the group listed in claim 11. As the Examiner admits, Sugimoto et al. '841 and Iimura et al. '330 disclose acetylcholine esterase inhibitors rather than sigma receptor binding agents. As discussed above, the Kato et al. reference does not overcome this deficiency.

To establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. (See MPEP 2143.03). As discussed above, the combination of Sugimoto et al. '841, Iimura et al. '330, and Kato et al. does not teach or suggest all the claim limitations of pending claims 11-12, 15, 18-20 and 22-24. Therefore, a *prima facie* case of obviousness has not been established, and withdrawal of the instant rejections is respectfully requested.

Applicants therefore respectfully submit that claims 11-12, 15, 18-20 and 22-24 clearly distinguish over the cited prior art of record.

CONCLUSION

Based upon the amendments and remarks presented herein, the Examiner is respectfully requested to issue a Notice of Allowance clearly indicating that pending claims 11-12, 15, 18-20 and 22-24 are allowed and patentable under the provisions of Title 35 of the United States Code.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey (Reg. No. 32,881) at the telephone number below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: APR 25 2008

Respectfully submitted,

for By _____ #42,874

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